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IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (DOING BUSINESS AS LABCORP),

Petitioner,

v.

METABOLITE LABORATORIES, INC., and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF THE AMERICAN HEART ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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Federal Constitution & Statutes

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35 U.S.C. § 103 16
35 U.S.C. § 284 4

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Miscellaneous

C. J. Boushey *et al.*, *A Qualitative Assessment of Plasma Homocysteine As A Risk Factor For Vascular Disease*, 274 J. AM. MED. ASSOC. 1049 (1995).....22
Stephen G. Breyer, *Genetic Advances and Legal Institutions*, 28 J. L. MED. & ETHICS 23 (2000).....11
Ralph Carmel *et al.*, *Update on Cobalamin, Folate, and Homocysteine*, 2003 HEMATOLOGY 62 (2003).....2
Robert Clarke *et al.*, *Hyperhomocysteinemia: An Independent Risk Factor for Vascular Disease*, 324 N. ENGL. J. MED. 1149 (1991).....20
GEORGE T. CURTIS, A TREATISE ON THE LAW OF PATENTS FOR USEFUL INVENTIONS § 124 (4th ed. 1873).....11
DIETARY REFERENCE INTAKES FOR THIAMIN, RIBOFLAVIN, NIACIN, VITAMIN B_6, FOLATE, VITAMIN B_{12}, PANTOTHENIC ACID, BIOTIN, AND CHOLINE (The National Academies Press 1998).....25
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Edward Felsenthal, *Medical Patents Trigger Debate Among Doctors*, WALL ST. J., Aug. 11, 1994, at B1, B6.....28
J. D. Finkelstein, *Homocysteine: A History in Progress*, 58 NUTRITIONAL REVIEWS 193 (2000).....19
J. B. Gibson *et al.*, *Pathological Findings in Homocystinuria*, 17 J. CLIN. PATHOL. 427 (1964).....20
HOMOCYSTEINE IN HEALTH AND DISEASE (Ralph Carmel & Donald Jacobsen eds., 2001).....19
1 ERNEST B. LIPSCOMB, WALKER ON PATENTS § 2:3 (3d ed. 1985).....10

TABLE OF AUTHORITIES (continued)

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M. Rene Malinow *et al.*, *Homocyst(e)ine, Diet, and Cardiovascular Diseases: A Statement for Healthcare Professionals From the Nutrition Committee, American Heart Association*, 99 CIRCULATION 178 (1999) 19, 21, 22, 26

Brian McCormick, *Just Reward or Just Plain Wrong? Specter of Royalties from Method Patents Stirs Debate*, AM. MED. NEWS, Sept. 5, 1994, at 3, 3. 28

Kilmer S. McCully, *Vascular Pathology of Homocysteinemia: Implications for the Pathogenisis of Arteriosclerosis*, 56 AM. J. PATHOL. 111 (1969) 20

O. Nygård *et al.*, *Total Homocysteine and Cardiovascular Disease*, 246 J. INTERNAL MED. 425 (1999) 20

1 WILLIAM C. ROBINSON, ROBINSON ON PATENTS §§ 133-143 (1890) 11, 12

Sudha Seshadri *et al.*, *Plasma Homocysteine as a Risk Factor for Dementia and Alzheimer's Disease*, 346 N. ENGL. J. MED. 476 (2002) 23

L. Stokes *et al.*, *Blood Levels of Homocysteine and Increased Risk of Cardiovascular Disease*, 160 ARCH. INTERN. MED. 422 (2000) 21

L. Joseph Su & Lenore Arab, *Nutritional Status of Folate and Colon Cancer Risk: Evidence From NHANES I Epidemiologic Follow-up Study*, 11 ANN. EPIDEMIOLOGY 65 (2001) 23, 24

Marianne Verhaar *et al.*, *Folates and Cardiovascular Disease*, 22 ARTERIOSCLER. THROM. VASC. BIOL. 6 (2002) 20, 21

S. E. Vollset *et al.*, *Plasma Total Homocysteine, Pregnancy Complications, and Adverse Pregnancy Outcomes: The Hordaland Homocysteine Study*, 55 OBSTETRICAL & GYNECOLOGICAL SURVEY 595 (2000) 23

Peter W. F. Wilson, *Homocysteine and Coronary Heart Disease*, 288 J. AM. MED. ASSOCIATION 2042 (2003) 2

TABLE OF AUTHORITIES (continued)

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Shumin M. Zhang *et al.*, *Plasma Folate, Vitamin B_6, Vitamin B_{12}, Homocysteine, and Risk of Breast Cancer*, 95 J. NAT. CANCER INST. 373 (2003).....23

STATEMENT OF INTEREST*

Amicus, the American Heart Association ("AHA"), is a nonprofit, national voluntary health organization with the mission of reducing disability and death from cardiovascular diseases and stroke. AHA's strategic goal, adopted in 1998, is to positively affect the general health and well-being of American society by helping to reduce cardiovascular diseases, stroke, and risk by 25 percent by 2010. This bold strategic goal responds to the sobering reality that as many as 930,000 of our fellow Americans—family, friends, and neighbors—are killed every year by these diseases, and many thousands more are disabled. Heart attacks and strokes devastate victims, families, and relationships, threatening life and bringing emotional upheaval and financial distress to all segments of American society.

Research shows that coronary heart disease, stroke, and risk can be best prevented if Americans take charge of their own health in close consultation with healthcare providers. AHA promotes individual healthcare responsibility by publishing guidelines regarding practical, sensible ways to protect health, advising Americans as to the risks of poor health, and teaching patients how to reduce those risks in partnership with their healthcare providers.

The AHA has no interest in taking sides in a commercial patent dispute. However, because the Court's decision in this case will have profound effects on the way in which healthcare professionals are able to render healthcare advice to patients dealing with cardiovascular diseases and stroke (among other disorders), *amicus* has a special interest in participating in the debate over whether a patent claim, which claims a simple two-step method for correlating test

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* No party other than *amicus* and its counsel authored this brief in whole or in part, and no person or entity, other than *amicus* and its counsel, has made a monetary contribution to the preparation or submission of this brief. Both parties have granted consent to the filing of this *amicus curiae* brief. Letters of consent are on file with the Clerk of the Court.

results using a basic, known scientific relationship, can trigger the exclusionary power of a United States patent so as to prohibit a physician from dispensing cardiovascular-related and other healthcare advice to patients. In addition, *amicus* holds a special position in the community of individuals affected by this patent in view of its interest in promulgating research and encouraging health testing, and is uniquely suited to provide the Court with what *amicus* believes will be helpful insights into the impact of this case on the healthcare profession and the patients served by that profession.

STATEMENT

1. Since the 1960s, epidemiological studies have shown a relationship between elevated blood levels of the amino acid homocysteine and the risk of coronary heart disease, stroke, and peripheral vascular disease. *See* Peter W. F. Wilson, *Homocysteine and Coronary Heart Disease*, 288 J. AM. MED. ASSOCIATION 2042, 2042-43 (2003). Plasma homocysteine levels are strongly influenced by diet, as well as genetic factors. The dietary components with the greatest effects are folic acid and vitamins B_6 and B_{12}, the latter of which contains the element cobalt and is thus known as cobalamin. Because the B vitamins assist in metabolizing homocysteine, scientists can directly assay homocysteine, along with other substances, in plasma to screen for cobalamin and folate deficiency. There are, in addition, multiple other reasons for plasma homocysteine levels to be elevated. *See generally* Ralph Carmel *et al.*, *Update on Cobalamin, Folate, and Homocysteine*, 2003 HEMATOLOGY 62, 62-81 (2003).

2. In the 1980s, scientific researchers at University Patents Inc. ("UPI"), the predecessor of respondent Competitive Technologies, Inc. ("CTI"), discovered that elevated levels of total homocysteine are closely associated with deficiencies in cobalamin or folate. UPI scientists applied for and received U.S. Patent No. 4,940,658 ("the

'658 patent"), which contains claims drawn to methods for assaying samples of body tissues to determine total homocysteine levels, as well as methods for both diagnosing and treating cobalamin and folate deficiency based on elevated total homocysteine. Pet. App. 2a-3a. Claim 13 of the '658 patent, at issue here, identifies a two-step "method for detecting a deficiency of cobalamin or folate in warm-blooded animals," comprising the following steps:

> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

Id. at 3a.

3. CTI licensed the '658 patent to respondent Metabolite Laboratories, Inc. ("Metabolite"), which in turn sub-licensed the patent to the predecessor-in-interest of petitioner Laboratory Corporation of America Holdings ("LabCorp"). Physicians ordered total homocysteine assays from LabCorp, which initially performed the assays under its sub-license by using the assay method set forth in the patent. In 1998, however, LabCorp began using a different assay method and stopped paying royalties to Metabolite. Metabolite then filed suit against petitioner for inducing patent infringement by the physicians and for breach of contract. *Id.* at 3a-4a.

4.a. Metabolite sued LabCorp for direct and indirect infringement of the '658 patent (and for breach of the sub-license agreement), alleging that LabCorp's performance of homocysteine tests using the alternative method induced and contributed to doctors' infringement of claim 13 of that patent. *Id.* The district court, pursuant to *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), issued a pre-trial order construing claim 13. The court defined "elevated" as "raised above the normal range." Pet. App. 29a, 32a. The court also defined "correlating" as meaning

"to establish a mutual or reciprocal relationship." *Id.* at 29a. Having construed the disputed claim terms, the case proceeded to trial before a jury. The jury returned a verdict against LabCorp for contributory and induced infringement, and for breach of the sub-license agreement. The jury assessed damages against LabCorp in the amount of $3,652,724.61 for breach of contract and $1,019,365.01 for infringement. *Id.* at 4a. The jury also found LabCorp's infringement to be willful, and returned a verdict in favor of plaintiffs on LabCorp's invalidity defenses. The district court entered judgment against LabCorp and awarded damages as assessed by the jury. *Id.* at 34a-39a.

b. After the trial, the district court denied LabCorp's motion for judgment as a matter of law on infringement, breach of contract, patent invalidity, and willful infringement. In light of the finding of willful infringement, the district court doubled the jury's infringement award to $2,038,730.02. *See* 35 U.S.C. § 284 (second paragraph). The district court also permanently enjoined LabCorp from using the alternative homocysteine-only test. Pet. App. at 34a-39a. LabCorp appealed.

c. A divided panel of the Federal Circuit affirmed. *Id.* at 1a-27a. Focusing on the correlating step of claim 13, the court of appeals held that "'correlating' means to relate the presence of an elevated total homocysteine level to either a cobalamin or folate deficiency, or both . . . and also to relate the absence of an elevated total homocysteine level to a deficiency in neither." *Id.* at 12a. Because "[t]he record shows that physicians order assays and correlate the results of those assays," the court of appeals held that physicians who ordered assays from petitioner after petitioner stopped making royalty payments had directly infringed the patent. *Id.* at 13a. The court further concluded that substantial evidence supported the jury's finding that petitioner intended to induce such infringement because petitioner provided total homocysteine assays to physicians, and encouraged the use of such assays to detect cobalamin and folate deficiency by

publishing and providing articles setting forth the correlation between elevated total homocysteine levels and cobalamin and folate deficiency. *Id.* at 15a.

The court of appeals rejected LabCorp's contentions that claim 13 is invalid on grounds of indefiniteness, lack of written description and enablement, anticipation, and obviousness. *Id.* at 15a-21a. In the course of rejecting LabCorp's anticipation and obviousness challenges to claim 13, the Federal Circuit specifically noted:

> In this case, the correlating step does not require computer technology or extensive computations. Instead, the record shows repeatedly that the correlating step is well within the knowledge of one of skill in this art. The correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step.

Id. at 18a.

Judge Schall concurred in part and dissented in part. *Id.* at 28a-33a. He "agree[d] with the majority's conclusions with respect to validity" of the patent, but would have construed claim 13 more narrowly than did the district court and the panel majority. *Id.* at 28a. Because "[t]he plain language of the claim requires 'elevated' levels of homocysteine," Judge Schall concluded that claim 13 is infringed only when a test reveals elevated levels, not when it reveals normal or low levels. *Id.* at 30a.

The Federal Circuit denied LabCorp's petition for rehearing and rehearing *en banc*. *Id.* at 40a-41a.

d. After calling for the views of the Solicitor General, this Court granted certiorari limited to question three of the Petition: "Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party simply to 'correlat[e]' test results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the

patent merely by thinking about the relationship after looking at the test result." 126 S. Ct. 601 (2005).

SUMMARY OF ARGUMENT

In this case, the Court is asked to resolve the extent of patentable subject matter under the Constitution and patent laws of the United States. The starting point for addressing this question is the basic truth that only inventions are patentable; laws of nature are not. Careful scrutiny of this principle, from this Court's earliest patent cases, *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853), and *The Telephone Cases*, 126 U.S. 1 (1888), through this Court's more recent pronouncements, *Parker v. Flook*, 437 U.S. 584 (1978), and *Diamond v. Diehr*, 450 U.S. 175, 185 (1981), limns the following rule: "[Patent] claims which *directly or indirectly preempt* natural laws or phenomena are proscribed, whereas claims which merely *utilize* natural phenomena via explicitly recited manufactures, compositions of matter or processes to accomplish new and useful end results define statutory inventions." *In re Bergy*, 596 F.2d 952, 988 (C.C.P.A. 1979) (Rich, J.), *vacated as moot*, 444 U.S. 1028 (1980) (emphasis added).

Application of this Court's existing precedent to claim 13 easily yields the conclusion that it contains nothing inventive. Rather, it seeks to claim a private right to exclude all others from utilizing a scientific correlation that the named inventors did not "invent."

If claim 13 of the '658 patent were held by this Court to cover patentable subject matter, it would grant respondents an exclusionary right that would prevent doctors from properly diagnosing and treating cardiovascular disease risk in their patients, not to mention other disorders—including even cobalamin (vitamin B_{12}) deficiency itself. It would forbid physicians from following the AHA's published Science Advisory for physicians in the course of patient treatment. And it would surely open the floodgates to a spate of similar patent applications in other areas of medical

diagnosis and treatment. The Court should maintain the proper balance in this area by reversing the judgment of the Federal Circuit and holding that claim 13 of the '658 patent claims no "invention" within the meaning of the Constitution and Patent Act.

ARGUMENT

U.S. Letters Patent 4,940,658, entitled "Assay for Sulfhydryl Amino Acids and Methods for Detecting and Distinguishing Cobalamin and Folic Acid Deficiency," contains 34 method claims. Claims 1-12 are drawn to particular methods of "assaying for the amount of one or more sulfhydryl amino acid species present in a given sample" (S.A. 30, column 41, lines 2-4); claims 13-28, 33, and 34 are drawn to methods for "detecting a deficiency of cobalamin or folate in warm-blooded animals" (*e.g.*, S.A. 30, column 41, lines 58-59); and claims 29-32 are drawn to methods of "treating a human for cobalamin deficiency" or "folic acid deficiency" (S.A. 31, column 43, lines 29-30; *id.*, column 44, lines 10-11, 17-18.)

This case involves independent claim 13 of the '658 Patent. That claim is a broadly drafted, two-step

> method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> [1] assaying a body fluid for an elevated level of total homocysteine; and
>
> [2] correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

S.A. 30, column 41, lines 58-65 (bracketed numbers added).

As to the first claimed step of "assaying," claim 13 is not, by its terms, limited to any particular type of assay. Other claims (14-17 and 19-28) *do* specify the type of assay required, however. *See* S.A. 30, column 42, lines 7-25; *id.*, column 42, line 37 to column 43, line 28. And as to the

second step of "correlating," both the district court and the Federal Circuit gave this claim step an exceedingly broad reading, concluding that it "only requires association of homocysteine levels with vitamin deficiencies. It requires no further correlation to confirm the relationship to vitamin deficiencies." Pet. App. 8a; *see also* J.A. 58-61 (district court *Markman* order). "The correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." Pet. App. 18a.

It is against this backdrop that this Court must consider the question presented.

I. CLAIM 13 OF THE '658 PATENT IMPROPERLY ATTEMPTS TO PATENT A LAW OF NATURE: THE BASIC, KNOWN NATURAL CORRELATION BETWEEN HOMOCYSTEINE AND B VITAMINS

A. Only "Inventions" Are Patentable; Laws Of Nature Are Not

The starting point for addressing the question presented in this case is the bargain struck by the Patent Clause of the Constitution: "The Congress shall have Power . . . To Promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries . . . ." U.S. CONST., art. I, § 8, cl. 8. The Constitution thus empowers Congress only to reward "Inventors" with an exclusionary right of limited term for their inventions. That right to exclude "is a property right; and like any property right, its boundaries should be clear." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 731 (2002). In keeping the boundaries of the right clear, the Constitution requires that the patent laws "Promote," rather than inhibit, the "Progress of Science and useful Arts" for the public interest. The constitutional requirement of "invention" is implemented by Section 101 of the Patent Act, whereby a patent may be granted to "[w]ho[m]ever invents

or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101.

Under the Constitution and the Patent Act, it is necessary—but not sufficient—that the applicant have made a "discovery" in order to obtain a patent. "Invention," too, is required.

> A discovery may be brilliant and useful, and not patentable. No matter through what long, solitary vigils, or by what importunate efforts, the secret may be wrung from the bosom of Nature, or to what useful purpose it may be applied. Something more is necessary. The new force or principle brought to light must be embodied and set to work, and can be patented only in connection or combination with the means by which, or the medium through which, it operates.

Morton v. New York Eye Infirmary, 5 Blatchf. 116, 17 F. Cas. 879, 884 (C.C.N.Y. 1862). Thus, as this Court stated in *Thompson v. Boisselier*, the beneficiary of a patent "must be an inventor *and* he must have made a discovery. The statute has always carried out this idea." 114 U.S. 1, 11 (1885) (emphasis added).

"The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." *Parker v. Flook*, 437 U.S. 584, 593 (1978). Careful scrutiny in this area is essential to the public interest, given "that scientific principles and laws of nature, even when for the first time discovered, have existed throughout time, define the relationship of man to his environment, and, as a consequence, ought not to be the subject of exclusive rights of any one person." *In re Meyer*, 688 F.2d 789, 795

(C.C.P.A. 1982) (citing *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1852)).

The additional requirement of "invention" ensures, among other things, that individuals cannot obtain exclusionary rights for fundamental scientific truths which existed *a priori*, but were "discovered" through exercise of the scientific act. That is why it is a commonplace that "[p]henomena of nature, though just discovered . . . are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972); *see also Diamond v. Diehr*, 450 U.S. 175, 185 (1981) ("laws of nature, natural phenomena, and abstract ideas" are not patentable subject matter).* "[T]he discovery of [a natural] phenomenon cannot support a patent unless there is some other inventive concept in its application." *Parker v. Flook*, 437 U.S. at 594; *see also* 1 ERNEST B. LIPSCOMB, WALKER ON PATENTS § 2:3, at 102 (3d ed. 1985) ("There must not only be an addition to knowledge but there must be produced as the result of the exercise of the inventive faculties a new and useful thing or result or a new process of producing an old thing or result."). In other words, patents are issued to "Inventors" only for their work in bringing about new means—inventions—to achieve certain useful ends.

B. Where A Patent Claim Would Confer A Private Property Right On All, Or A Substantial Part, Of A Natural Law Or Phenomenon, It Is Invalid

It is easy to state the principle that laws of nature or natural phenomena are not patentable, while inventions that merely utilize such scientific truths are patentable. Yet, "the

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* *Accord, e.g., Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980); *Parker v. Flook*, 437 U.S. 584, 589 (1978); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939); *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1852); *Wall v. Leck*, 66 F. 552, 558 (9th Cir. 1895).

line between a patentable 'process' and an unpatentable 'principle' is not always clear." *Parker v. Flook*, 437 U.S. at 589. The harder question arises when a patent claim that purports to go beyond the scientific truth itself nonetheless threatens to grant private exclusionary rights over many (or any) uses of that scientific truth. *See, e.g.*, Stephen G. Breyer, *Genetic Advances and Legal Institutions*, 28 J. L. MED. & ETHICS 23, 27 (2000) ("The most difficult question is deciding [whether] products of [] research reflect only discovery of an existing aspect of nature, like Einstein's discovery of the principles of relativity, [or whether] they amount to a protectable invention or useful device."); GEORGE T. CURTIS, A TREATISE ON THE LAW OF PATENTS FOR USEFUL INVENTIONS § 124 (4th ed. 1873) (describing the question as "how far a discovery or invention which may first disclose and practically embody some truth in physics or some law in the operation of the forces of nature, for a useful purpose, is capable of being carried in the exclusive privileges secured by the grant of letters patent"). The proper answer to this question should be this: Where a patent claim would confer a private exclusionary right on all, or a substantial part of, a natural phenomenon or law of nature, it is invalid.

William C. Robinson's seminal 1890 treatise described the nature of the inventive act and exhaustively explored the bases for the prohibition against patenting laws of nature or natural phenomena. 1 ROBINSON ON PATENTS §§ 133-143 (1890). Robinson recognized, over a hundred years ago, the line between laws of nature and inventions that merely employ those laws:

> In one sense, the word "principle" denotes the physical force employed by an invention. The other appellations given to this force are very numerous, and most of them are wholly inappropriate. It has been called "an elementary truth," "a principle of science," "a property of matter," "a law of nature," the "root and ground of science;" but the idea which

> underlies these phrases is sufficiently apparent, and is neither less nor more than that of some natural power or energy, which operates with uniformity under given circumstances, and may thus be contemplated as obedient to law. A principle, in this sense, is a necessary factor in every means which produces physical effects, whether such means be natural or artificial, and it is generally this which makes the chief impression on the senses of the observer; but it is in itself no true invention, nor can it be protected by a patent.

Id. § 135, at 193-95 (emphasis added) (footnote omitted).

Two cases decided by this Court in the years leading up to Robinson's treatise serve as the polestars that have long defined the line between patentable and unpatentable subject matter where laws of nature or natural phenomena are involved.

At one end of the spectrum, and helping to define the scope of what is not patentable, is the landmark Telegraph Case, *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853). There, Samuel Morse had received a patent for an apparatus for accomplishing the transmission of signals from a distance to an electromagnetic telegraph. *Id.* at 63. When Morse sued for patent infringement, the patent was challenged as not drawn to patentable subject matter. *Id.* In the Eighth Claim of the patent, Morse claimed rights to all uses of electromagnetism for sending signals over distance:

> Eighth. I do not propose to limit myself to the specific machinery or parts of machinery described in the foregoing specification and claims; the essence of my invention being the use of the motive power of the electric or galvanic current, which I call electro-magnetism, *however developed*, for marking or printing intelligible characters, signs, or letters at any

> distance, being a new application of that power of which I claim to be the first inventor or discoverer.

Id. at 112 (emphasis added).

This Court held the Eighth Claim invalid, because it was not limited to the actual machinery Morse invented, but was instead drawn to give Morse exclusionary rights over the work of others as they subsequently employed the principle of electromagnetism in various machines and processes. *See id.* ("It is impossible to misunderstand the extent of this claim. [Morse] claims the exclusive right to every improvement . . . ."). As this Court noted, if such a claim were to

> be maintained, it matters not by what process or machinery the result is accomplished. For aught that we know of some future inventor, in the onward march of science, may discover a mode . . . without using any part of the process or combination set forth in the plaintiff's [claim] . . . But yet if it is covered by this patent the inventor could not use it, nor the public have the benefit of it without the permission of the patentee. . . . [Such a claim would amount to] an exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent.

Id. at 113. Morse's Eighth Claim was thus struck down as improperly seeking an exclusionary property right in all uses of the underlying natural phenomenon of electromagnetism, not in his specific invention itself.

At the other end of the spectrum, and helping to define when merely using natural phenomena as a portion of an invention *is* patentable, is this Court's decision, twenty-five years later, in *The Telephone Cases*, 126 U.S. 1 (1888). Those cases involved the patentability of Alexander Graham Bell's invention, the telephone. Bell had discovered how to use electrical current to transmit voice signals by means of a

device that turned sound waves into electrical current, which was then transmitted over distance to a decoding device that transformed the waves back into sound. *Id.* at 531-35. Bell's Fifth Claim sought to patent "[t]he method of, and apparatus for, transmitting vocal or other sounds telegraphically, *as herein described*, by causing electrical undulation, similar in form to the vibrations of the air accompanying the said vocal or other sounds, substantially set forth [in the patent]." *Id.* at 531 (emphasis added).

Bell's opponents urged that he was—like Morse's Eighth Claim, *Morse*, 56 U.S. (15 How.) at 112—seeking to patent the essential mechanism of converting electricity into sound for all applications and with all devices. *The Telephone Cases*, 126 U.S. at 531. This Court held, however, that Bell was not claiming all uses of electricity converted to sound waves; rather, he was merely claiming the particular art, set forth in his patent, that utilized the principle of "controlling the force [of electricity] as to make it accomplish the purpose" of transmitting speech. *Id.* at 534. Bell was thus not claiming the principle itself, but was claiming his particular method and apparatus for utilizing that principle in a new and useful way. This Court decided that, because of the limiting clause in the claim—"as herein described"—the claim was necessarily cabined by Bell's apparatus. This result was in contrast to that in *Morse*, where the inventor sought to capture for himself all future developments through a broad method claim describing electromagnetism "however developed." *Id.* at 537-38.

This Court's cases, before and after, are consistent with the approach of *O'Reilly v. Morse* and *The Telephone Cases*. In *Le Roy v. Tatham*, 55 U.S. (14 How.) 156 (1852), the Court held that the practical application of a newly-discovered principle—a certain property of lead that it would form a bond if poured under certain pressure and temperature conditions—could be patented, but only in the form of a specific product or process that was itself new. *Id.* at 175-76. In *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306

U.S. 86, 94 (1939), the Court held, regarding a patent application for a certain type of antennae, that "[w]hile a scientific truth, or the mathematical expression of it, is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be." *Id.* at 93. In *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), the Court held that an inventor claiming a bacterial species that exhibited the property of mutual non-inhibition could not patent the bacteria, as it was merely a claim for a natural phenomenon itself, especially considering that his was not a discovery that applied "the law of nature to a new and useful end." *Id.* at 130. In *Parker v. Flook*, 437 U.S. 584 (1978), the Court disallowed a patent claiming methods for updating alarm limits and held that "if a claim is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is nonstatutory." *Id.* at 595 (internal quotation marks and citation omitted). In *Gottschalk v. Benson*, 409 U.S. 63 (1972), the Court held that a mere procedure for solving a math problem is not patentable, as it was a method for a general, non-specific, and non-inventive purpose. *Id.* at 67-68. In *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), the Court upheld a human-engineered microorganism as patentable, under 35 U.S.C. § 101, because it was encompassed by the rule of "invention" that "anything under the sun that is made by man" is patentable. *Id.* at 309. Finally, in *Diamond v. Diehr*, 450 U.S. 175 (1981), the Court held that although a mathematical formula embodied in a software program might not qualify for patent protection on its own, application of the formula to perform a new and useful process—in *Diehr*, a process for curing synthetic rubber—did qualify for patent protection. *Id.* at 191-93.

Consistent with these precedents, one of the Federal Circuit's predecessor courts, the Court of Customs and Patent Appeals, attempted to distill this Court's caselaw into a useable guideline for making this ultimately judicial

determination. As the late Judge Rich wrote for that court: "The common thread throughout [this Court's] cases is that [patent] claims which *directly or indirectly preempt* natural laws or phenomena are proscribed, whereas claims which merely *utilize* natural phenomena via explicitly recited manufactures, compositions of matter or processes to accomplish new and useful end results define statutory inventions." *In re Bergy*, 596 F.2d 952, 988 (C.C.P.A. 1979), *vacated as moot*, 444 U.S. 1028 (1980) (emphasis added). There is much to recommend in the *In re Bergy* formulation crafted by Judge Rich—it is wholly on par with this Court's precedents; it is consistent with the other requirements of the Patent Act (such as novelty, *see* 35 U.S.C. § 102, and obviousness, *see* 35 U.S.C. § 103); and it provides a calibrated filter for sorting truly inventive processes from non-inventive efforts to create private exclusionary rights in scientific truths.

C. Applying These Standards, Claim 13 Is Plainly Invalid

As George Ticknor Curtis and Justice Breyer separately recognized over a hundred years apart from one another, the question of patentability where natural laws or phenomena are involved frequently presents weighty and difficult issues. This case does not. Indeed, when one considers the dispositive difference between Morse's unpatentable telegraph claim and Bell's patentable telephone claim, and compares those polestars to claim 13 of the '658 patent, this case becomes an easy one.

As explained above, the dispositive difference of patentability between the Morse and Bell patent claims was that Bell's was limited to the precise apparatus "as herein described"—*i.e.*, the telephone, *The Telephone Cases*, 126 U.S at 531—whereas Morse's sought to claim all uses of electromagnetism "for marking or printing intelligible characters, signs, or letters at any distance," *O'Reilly v. Morse*, 56 U.S. (15 How.) at 112. The Brief for the United

States as *Amicus Curiae*, although urging that the issue required further factual development, acknowledged that claim 13 could not possibly be patentable if—analogous to Morse's patent—it "comprises every substantial practical application of the natural relationship between elevated total homocysteine and deficiencies in the B vitamins." (U.S. Br. at 17) Respondents' Brief in Opposition similarly attempted to cabin this case as more like Bell's than Morse's, urging that "the step of assaying for total homocysteine" was "a further distinct and physical step" that avoided granting Metabolite a "monopoly on a basic scientific step." (Opp. at 9)

But there is no serious argument available that the "assaying" step of claim 13 is itself in any way "inventive." Indeed, although the '658 patent includes extensive claims directed to precise (and, it appears, truly inventive) methods for conducting assays (*e.g.*, claims 1-12), claim 13 requires only "assaying a body fluid for an elevated level of total homocysteine." S.A. 30, column 41, lines 61-62. Comparison with claim 14 confirms the breadth of claim 13—claim 14 is identical in every way to claim 13, except for the additional requirement that the assay be performed "according to the method of claim 7," which itself is ultimately dependent on claim 1—which in turn sets forth a specific five-step method of performing such an assay. S.A. 30, column 42, line 2; *id.*, column 41, lines 34-35; *id.*, column 41, lines 2-19. Claim 13, by contrast, says nothing more than (1) "measure," and (2) "correlate that measurement with a scientific truth"—the relationship between homocysteine levels and cobalamin and folic acid deficiencies.

The analogy to *Morse* is striking. There, Samuel Morse sought exclusionary rights to the use of electromagnetism not in all of its possible applications, but only within the realm of "marking or printing intelligible characters, signs, or letters at any distance." *O'Reilly v. Morse*, 56 U.S. (15 How.) at 112. This further "marking or printing" limitation

did not save his Eighth Claim from a holding of unpatentability, as he was still in effect attempting to claim something that he did not invent. Here, similarly, the named inventors on the '658 patent did not invent the correlation between elevated homocysteine and cobalamin deficiencies; that law of nature existed *a priori*. Nor did those named inventors invent every potential method of "assaying a body fluid"—yet that is exactly what claim 13 seeks to protect.

Claim 14, by contrast, is exactly the same as claim 13, except that it requires the step of "assaying a body fluid" to be performed according to the inventive assaying method set forth in other claims of the '658 patent. That claim, it appears, is much more like the appropriately inventive Fifth Claim of the Alexander Graham Bell Patent, which claimed only the application of electricity converted into sound waves via Bell's claimed apparatus—the telephone. *See The Telephone Cases*, 126 U.S. at 531.

In sum, application of this Court's existing precedent to claim 13 easily yields the conclusion that it contains nothing inventive. Rather, it seeks to claim a private right to exclude all others from utilizing a scientific correlation that the named inventors did not "invent." *See Parker v. Flook*, 437 U.S. at 585, 593 n.15 ("The only novel feature of the method . . . [merely] reveals a relationship that has always existed").

II. SUSTAINING CLAIM 13 OF THE '658 PATENT WOULD HAVE DEVASTATING EFFECTS ON PATIENT HEALTHCARE

If claim 13 of the '658 patent were held by this Court to cover patentable subject matter, it would grant respondents an exclusionary right that would prevent doctors from properly diagnosing and treating cardiovascular disease risk in their patients. And it would surely open the floodgates to a spate of similar patent applications in other areas of medical diagnosis and treatment. These consequences can be avoided by holding that claim 13 of the '658 patent claims nothing inventive.

The AHA has no interest in taking sides in a commercial patent dispute. But it does have a profound interest, consistent with its mission and strategic goal, in ensuring that this particular patent claim is not allowed to interfere with appropriate diagnosis, care, and treatment of cardiovascular health. As noted above, the known relationship among homocysteine levels, increased cardiovascular risk, and vitamin B deficiency allows physicians to screen their patients for risk of heart disease by obtaining homocysteine levels, assessing to see whether elevated homocysteine levels are due to cobalamin or folate deficiency, and then seeking to reduce those increased cardiovascular risks by appropriate treatments, such as prescribing B vitamins and folic acid to mediate those levels. The AHA has issued a Science Advisory addressing homocysteine testing and subsequent treatment. *See* M. René Malinow *et al.*, *Homocyst(e)ine, Diet, and Cardiovascular Diseases: A Statement for Healthcare Professionals From the Nutrition Committee, American Heart Association*, 99 CIRCULATION 178, 178-82 (1999).

A. Homocysteine Testing Is Important For Assessing Patient Risk For Cardiovascular And Other Diseases, And Is Used For Guiding Treatment Of Those Diseases

Homocysteine is a sulphur-containing amino acid that is closely related to the essential amino acid methionine. *See* J. D. Finkelstein, *Homocysteine: A History in Progress*, 58 NUTRITION REVIEWS 193, 193-204 (2000). Methionine is an indispensable protein building block that cannot be produced by the body, must be provided by the diet, and supplies sulfur and other compounds required by the body for normal metabolism and growth. *Id.* Homocysteine is also related to the nonessential protein building block cysteine, which can be made in the human body. *See generally* HOMOCYSTEINE IN HEALTH AND DISEASE (Ralph Carmel & Donald Jacobsen eds., 2001).

An association between elevated homocysteine levels and human disease was first suggested by researchers in the 1960s. *See* J. B. Gibson *et al.*, *Pathological Findings in Homocystinuria*, 17 J. CLIN. PATHOL. 427, 427-37 (1964). At that time, researchers found that high homocysteine concentrations in the blood were associated with premature cardiovascular disease. *Id.* In 1969, homocysteine was affirmatively correlated with the risk of cardiovascular disease and stroke. *See* Kilmer S. McCully, *Vascular Pathology of Homocysteinemia: Implications for the Pathogenisis of Arteriosclerosis*, 56 AM. J. PATHOL. 111, 111-28 (1969). During the last 15 years, it has been repeatedly documented, through epidemiological studies, that even a moderately elevated homocysteine level in blood serum or plasma is a strong and independent risk factor for cardiovascular disease and stroke. *See, e.g.*, Robert Clarke *et al.*, *Hyperhomocysteinemia: An Independent Risk Factor for Vascular Disease*, 324 N. ENGL. J. MED. 1149, 1155 (1991); O. Nygård *et al.*, *Total Homocysteine and Cardiovascular Disease*, 246 J. INTERNAL MED. 425, 425-54 (1999).

Several studies have found that there is a relationship between the blood levels of B vitamins and homocysteine concentrations in the blood. *See, e.g.*, Marianne Verhaar *et al.*, *Folates and Cardiovascular Disease*, 22 ARTERIOSCLER. THROM. VASC. BIOL. 6, 6-13 (2002). Because the B vitamins assist in metabolizing homocysteine, scientists directly assay homocysteine (and other substances) in order to screen for, among other things, cobalamin (vitamin B_{12}) and folate (vitamin B_9) deficiencies. It is believed that the body regulates the homocysteine concentration in the body with the aid of several B vitamins, including folic acid. *Id.* Apart from a genetic predisposition, a shortage of these vitamins can also lead to an increased concentration of homocysteine in the blood. *Id.* However, cobalamin deficiency accounts for only a minority of elevated homocysteine levels; inborn errors of homocysteine metabolism, renal insufficiency, hypothyroidism, alcohol

abuse, enzyme polymorphisms, and other conditions account for the rest.

Cardiovascular Diseases. In the area of cardiovascular diseases, homocysteine testing is used to assess the level of risk for heart attack or stroke. Recent findings indicating graded association of plasma homocysteine levels with cardiovascular risk suggest that the availability of laboratory testing for plasma homocysteine levels can improve the assessment of risk, particularly in patients with a personal or family history of cardiovascular disease. Likewise, homocysteine testing can be ordered as part of a general cardiac-risk assessment, depending on the patient's age and other risk factors. It may also be ordered following a heart attack or stroke to help guide treatment.

Studies have suggested that people who have elevated homocysteine levels have a much greater risk of heart attack or stroke than those with average levels. *See* Verhaar *et al.*, *supra*, at 6-13. "It's pretty clear from most cross-sectional and case-controlled studies and some prospective studies that hyperhomocysteinemia increases the risk for not only myocardial infarction, but also coronary artery disease, peripheral vascular disease, stroke, cerebrovascular disease, restenosis of coronary arteries that have undergone balloon angioplasty, and even death from coronary artery disease." L. Stokes *et al.*, *Blood Levels of Homocysteine and Increased Risk of Cardiovascular Disease*, 160 ARCH. INTERNAL MED. 422, 422-34 (2000). At present, the AHA has not established a direct correlation between homocysteine levels and heart attacks, nor evidence that lowering these levels will with certainty reduce the rate of cardiovascular events, but the AHA does acknowledge strong evidence of a relationship between homocysteine levels and cardiovascular risk. *See* Malinow *et al.*, *supra*, at 178-82.

Since measuring homocysteine levels to determine cardiac risk is a relatively new use for the test, a standardized

interpretation of the measured value has yet to be determined. *Id.* In many people, homocysteine levels can be decreased by taking extra levels of folic acid, vitamin B_{12}, and vitamin B_6—the B-complex vitamins that drive homocysteine metabolism. In others, different results will obtain. Nonetheless, because it may well help (and should not hurt), many doctors and researchers consider folic acid supplementation to be an effective strategy for reducing the quantity of homocysteine in the blood, possibly lessening the risk of cardiovascular and other ailments attributable to homocysteine.

The AHA has a direct interest in the results of ongoing research in this field, and in having its view of the science in this field disseminated throughout the healthcare industry. This is so because a mild to moderate elevation in homocysteine can increase the risk of coronary artery disease by 2.5 times. Projections from a number of small studies suggest that lowering homocysteine by only 5 µmol/L may reduce the death rate from coronary artery disease by 10 percent, C. J. Boushey *et al.*, *A Quantitative Assessment of Plasma Homocysteine As A Risk Factor For Vascular Disease,* 274 J. AM. MED. ASSOC. 1049, 1049-57 (1995), although this has not yet been demonstrated conclusively in large, long-term randomized clinical trials. The volume of homocysteine testing has grown steadily since the early 1990s, when prospective trials and case-controlled studies started showing that this amino acid was associated with an increased risk for cardiovascular disease. Indeed, the record in this case reflects that as these trials and studies became known, and the AHA published its "Science Advisory on Homocysteine, Diet and Cardiovascular Diseases" for physicians, the demand for homocysteine tests "seemed to skyrocket," and petitioner "couldn't keep up with the work" occasioned by all of the physician requests for homocysteine assays. J.A. 168 [Tr. 1423].

Other Diseases. Significantly, elevated homocysteine levels may be indicators of diseases and maladies beyond

cardiovascular disease and stroke. Elevated homocysteine levels have also been associated with adverse pregnancy outcomes, such as spontaneous early abortion and birth defects. *See generally* S. E. Vollset *et al.*, *Plasma Total Homocysteine, Pregnancy Complications, and Adverse Pregnancy Outcomes: The Hordaland Homocysteine Study*, 55 OBSTETRICAL & GYNECOLOGICAL SURVEY 595 (2000). Assaying for B vitamin and folate deficiencies and then supplementing any noticed folate deficiencies with folic acid during the pre-conception period and pregnancy has been shown to substantially decrease the incidence of birth defects, and may reduce the incidence of some pregnancy complications, such as spontaneous abortions. *Id.*

Some studies have also identified an association between elevated homocysteine levels and impaired cognitive performance and dementia, which may portend findings that diseases such as Alzheimer's may be in some ways influenced by homocysteine levels in the body. *See* Sudha Seshadri *et al.*, *Plasma Homocysteine as a Risk Factor for Dementia and Alzheimer's Disease*, 346 N. ENGL. J. MED. 476, 476-83 (2002). Even moderately elevated levels of homocysteine in the body may be associated with an increased risk of developing dementia, or with an increase in the rate of disease progression in those individuals already afflicted. *Id.* While more studies need to be done, reduction of homocysteine levels has been shown to have a positive impact on cognitive performance in elderly individuals with mild cognitive impairment, and to increase regional cerebral blood flow. *Id.*

There is also current research being done on the association between cancer, particularly breast and colon cancers, and impaired homocysteine metabolism. *See* Shumin M. Zhang *et al.*, *Plasma Folate, Vitamin B_6, Vitamin B_{12}, Homocysteine, and Risk of Breast Cancer*, 95 J. NAT. CANCER INST. 373, 373-80 (2003); L. Joseph Su & Lenore Arab, *Nutritional Status of Folate and Colon Cancer Risk: Evidence From NHANES I Epidemiologic Follow-up Study*,

11 ANN. EPIDEMIOLOGY 65, 65-72 (2001). Finally, researchers have also noticed an association between homocysteine levels and depression and other neuropsychiatric disorders. *See* M. Fava *et al.*, *Folate, Vitamin B_{12}, and Homocysteine in Major Depressive Disorder*, 154 AM. J. PSY. 426, 428 (1997). More work remains to be done in these and other areas in order to develop strategies for further assessing these correlations (and suspected connections) between homocysteine and various physical and neuropsychiatric diseases, as well as adopting strategies to improve the healthcare of individuals with elevated homocysteine levels in light of such findings. Even so, physicians are already treating identified vitamin B deficiencies with vitamin supplements with the goal of reducing homocysteine levels and thereby improving overall patient health.

In the AHA's specific area of interest, homocysteine testing is becoming an important tool for assessing cardiovascular risk. Screening of homocysteine levels in the appropriate at-risk patients, followed by prophylactic vitamin supplementation, while still being investigated, is commonly undertaken by physicians to reduce this adverse risk factor.

B. Claim 13 Of The '658 Patent, If Left Standing, Would Prevent Doctors From Following The AHA's Advisory

If upheld, the Federal Circuit's decision would prohibit doctors from following the suggestions in the AHA's Science Advisory in their care of cardiac patients. That would be a profoundly regrettable result for patient care.

As outlined above, there is widespread epidemiological evidence demonstrating a correlation between plasma homocysteine and cardiovascular disease. However, there is at present no definitive study suggesting that reducing homocysteine levels by increasing patient intake of folic acid via diet or vitamin supplement will in fact reduce cardiovascular disease risk. In light of the available data, the

American Heart Association has published a Science Advisory regarding homocysteine testing, with comments as follows.

- Until results of controlled clinical trials become available, population-wide screening is not recommended, and emphasis should be placed on meeting current recommended daily allowances for folate, as well as vitamins B_6 and B_{12}, by intake of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals.
- For patients at a high risk of cardiovascular disease, either through genetic or environmental factors, a strategy may include screening in selected patients (*e.g.*, those with personal or family history of premature cardiovascular disease; those with renal dysfunction or renal failure, malnutrition, hypothyroidism; those taking certain medications; and those with recent nitrous oxide exposure) to uncover fasting plasma homocysteine levels associated with augmented risk status.
- After confirming high homocysteine concentration, it is important to check the vitamin status, owing to the inverse relationships reported between homocysteine and blood levels of folate, B_6, and B_{12}, although it should be recognized that there is currently no firm basis for recommending specific therapeutic targets for homocysteine levels. Measuring the level of plasma methylmalonic acid is the next step in determining vitamin B_{12} deficiency. A useful algorithm for the diagnosis of vitamin deficiency, beyond direct determination of blood levels of this vitamin, is described in DIETARY REFERENCE INTAKES FOR THIAMIN, RIBOFLAVIN, NIACIN, VITAMIN B_6, FOLATE, VITAMIN B_{12}, PANTOTHENIC ACID, BIOTIN, AND CHOLINE (The National Academies Press 1998).

- In high-risk patients, it may also be advisable to increase their intake of vitamin fortified foods and/or to suggest the daily use of supplemental vitamins, *i.e.*, 0.4 mg of folic acid, 2 mg of vitamin B_6, and 6 mg of vitamin B_{12}, with appropriate medical evaluation and monitoring.
- Treatment may include higher doses of those vitamins according to the response of homocysteine. However, such treatment is still considered experimental, pending results from intervention trials showing that homocysteine lowering favorably affects the evolution of arterial occlusive diseases.

See Malinow *et al.*, *supra*, at 178-82.

AHA has a profound concern that, if the Federal Circuit's judgment is not reversed, physicians will not legally be able to follow the AHA Advisory set forth above. AHA encourages physicians who order homocysteine assays to then "correlate" those results to determine patient risk and the appropriate course of treatment. Given the scope of claim 13 as upheld to date by the courts in this case, it is difficult to see how a doctor could prescribe vitamin therapy to lower a patient's elevated homocysteine level without also making the correlation that infringes that patent claim. Indeed, it is difficult to see how a doctor could examine a patient's elevated homocysteine level and merely *consider* the possibility that the elevated level was due to cobalamin deficiency (a relationship the doctor would have learned in medical school) without similarly infringing claim 13.

But the adverse effect of the courts' decisions in this case are obviously not limited to cardiac care. In view of the several other correlations between homocysteine levels and other conditions, diseases, and maladies, in areas such as cancer, pregnancy, neuropsychiatric disorders, and dementia, claim 13 of the '658 patent creates the very real potential for private capture of every possible manner and use of measuring homocysteine levels in human beings. Such a

result could have tragic consequences indeed for the health of our Nation's citizens.

C. Reversing The Judgment Of The Federal Circuit Will Correctly Balance The Appropriate Rewards Of The Patent System With The Needs For Proper Patient Care

There can be no doubt that a properly calibrated patent system creates positive incentives for the development of new and useful pharmaceuticals, medical devices, and diagnostic and treatment methods, all to the benefit of public health and safety. *See, e.g., Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 63-64 (1998). But when, as here, a purported "inventor" is allowed to claim exclusionary rights over something that is truly noninventive, but instead is an *a priori* scientific truth, the "carefully crafted bargain" of the patent system, *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 151 (1989), is distorted beyond both congressional intent and its constitutional moorings.

It is important that this Court maintain this proper balance. The simple two-step "measure, then correlate" process set forth in claim 13 of the '658 patent, which requires only an assay done by any method under the sun, followed by "a simple conclusion that a cobalamin/folate deficiency exists" (Pet. App. 18a), is, under no reasonable understanding of the word, an "invention." Yet many of the other claims of the '658 patent, including claim 14, appear to set forth true novel and useful "inventions"—specific new methods for performing assays that merely utilize the scientific truth—within the meaning of the Constitution and the Patent Laws. That line—between claim 13 and claim 14—is indicative of the careful balance in the patent system that this Court's decision should maintain.

The importance of maintaining this balance cannot be overstated. In the three decades following the 1950s, very few medical-procedure patents were issued. *See, e.g.,*

Edward Felsenthal, *Medical Patents Trigger Debate Among Doctors*, WALL ST. J., Aug. 11, 1994, at B1, B6. More recently, patent attorneys have estimated that the Patent and Trademark Office (PTO) grants at least a dozen medical procedure patents each week. Brian McCormick, *Just Reward or Just Plain Wrong? Specter of Royalties from Method Patents Stirs Debate*, AM. MED. NEWS, Sept. 5, 1994, at 3, 3. And our very simple search of an electronic database of U.S. patents conducted shortly before filing this brief disclosed over 300 patents containing method claims that include steps of "assaying" and "correlating."

Obviously, many, if not most or all of these 300-plus patents set forth actual inventions and merely utilize the scientific truths as a component of the invention (in the same way that *amicus* believes that claim 14 of the '658 patent sets forth an actual, patentable invention). But this Court's careful guidance is needed to ensure that the PTO is not, after the Court's decision in this case, inundated with patent claims similar to claim 13 that claim nothing more than assays plus correlations of those assay results with immutable scientific truths. That would have disturbing consequences for the patent system, for medical diagnoses, and for patient health care. The Court should maintain the proper balances in these areas by reversing the judgment of the Federal Circuit and holding that claim 13 of the '658 patent claims no "invention" within the meaning of the Constitution and the Patent Act.

CONCLUSION

For these reasons, *amicus* respectfully urges the Court to reverse the decision below.

Respectfully submitted,

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